

REMARKS

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

Initially, applicants would like to note that the present amendment is being submitted in compliance with "Amendments In A Revised Format Now Permitted", 1267 OG 4 (February 25, 2003). Pursuant to this notice, the requirements of 37 C.F.R. § 1.121 have been waived.

The rejection of claims 1-9 and 68-76 under 35 U.S.C. § 112, second paragraph, for indefiniteness is rendered moot with respect to claims 1-9 (canceled without prejudice) and is respectfully traversed with respect to claims 68-76 in view of the above amendments.

It is noted, however, that in addition to deleting the term "variant", applicant has amended claim 68 to specify as an alternative within the Markush Group "a polypeptide comprising the amino acid sequence of SEQ ID NO: 16 or 17." Applicant submits that this language effectively covers those variants of BVR that possess one of the recited sequences. In particular, applicant notes that the present application does indeed identify a number of variants of BVR in the mutational studies identified in Example 1 (identifying active centers in BVR that are responsible for NADH- and NADPH-specific activities of BVR). A number of those variants possess reductase activity as described in Example 1. Considering Examples 1 and 3 together, Example 3 demonstrates peptide fragments of BVR (that necessarily lack reductase activity but) possess protein kinase C regulatory activity

The rejection of claims 1-9, 68-70, and 74-76 under 35 U.S.C. § 112, first paragraph, for lack of written descriptive support is rendered moot with respect to claims 1-9 (canceled without prejudice) and is respectfully traversed with respect to claims 68-70 and 74-76.

The PTO has taken the position that the present application fails to provide written descriptive support for the claimed method of regulating protein kinase C activity because descriptive support is lacking for the genus of biliverdin reductase ("BVR"). Applicant disagrees.

The basis for the PTO's argument is that because some proteins can have distinct functions lost or modified with only slight changes in the amino acid sequence,

applicant's description of three species of the genus of mammalian BVR is insufficient. Applicant disagrees.

The present application identifies three species of mammalian BVR (SEQ ID NOS: 1, 3, and 4). The present application also describes the functional domains of BVR at page 16, lines 8-33; describes preparation of BVR fragments and identifies exemplary fragments at page 17, line 22 to page 18, line 28; and describes preparation of BVR variants and identifies exemplary variants at Example 1 and at page 18, line 29 to page 19, line 24. In addition, Example 3 describes the identification of polypeptide fragments of BVR that possess protein kinase C regulatory activity. From the foregoing, it should be appreciated that the present application defines not only specific BVR fragments and variants, including those that have demonstrated efficacy in regulating protein kinase C activity, but also how one of ordinary skill in the art can identify other fragments or variants that can regulate protein kinase C activity.

As further evidence that the present application does, in fact, provide written descriptive support for the genus of mammalian BVR, attached hereto as Exhibit A is a copy of Genbank Accession NP_080954, which reports the amino acid sequence of mouse BVR, and as Exhibit B is an alignment of human, rat, and mouse BVR sequences (performed using alignment software at <http://cbcsrv.watson.ibm.com/Tmsa.html> on its default settings for "Exact Discovery"). As shown in the alignment, mouse BVR (bottom row) possesses at positions 274-280 the amino acid sequence of SEQ ID NO: 34, which possesses protein kinase C regulating activity. This is identical to the sequence at positions 275-281 of human BVR. Therefore, one of ordinary skill in the art would expect mouse BVR to similarly possess protein kinase C regulatory activity.

Based on the disclosure of three species of mammalian BVR and the disclosure of protein kinase C regulatory regions within BVR, as well as the demonstration that a fourth species shares a protein kinase C regulatory region in common with the other three species, one of ordinary skill in the art would have understood that applicants were in possession of the genus of mammalian BVR for use in regulating protein kinase C activity. The PTO has failed to demonstrate otherwise and, thus, has failed to carry its burden. Therefore, the rejection of claims 68-70 and 74-76 for lack of written descriptive support is improper and should be withdrawn.

The rejection of claim 1 under 35 U.S.C. § 112, first paragraph, for lack of written descriptive support is rendered moot in view of the cancellation of claim 1 (without prejudice).

The rejection of claims 1-9, 68-70, and 74-76 under 35 U.S.C. § 112, first paragraph, for lack of enablement is rendered moot with respect to claims 1-9 (canceled without prejudice) and is respectfully traversed with respect to claims 68-70 and 74-76.

The subject matter of claim 68 relates to a “method of regulating protein kinase C activity comprising: contacting protein kinase C with a mammalian biliverdin reductase, a fragment thereof with protein kinase C regulatory activity, or a polypeptide comprising the amino acid sequence of SEQ ID NO: 16 or 17, under conditions effective to regulate protein kinase C activity.”

The only basis of rejection applicable to claim 68 relates to the use of “any biliverdin reductase, active fragment or variant thereof” (office action at page 6). Claim 68 presently recites mammalian BVR and, for the reasons noted above, one of ordinary skill in the art would be fully able to identify other mammalian BVR. Determining whether such mammalian BVR possess BVR activities can be carried out as described in Example 1 and determining whether such mammalian BVR possess protein kinase C regulating activity can be carried out as described in Example 3. Therefore, one of ordinary skill in the art is fully able to determine whether another mammalian BVR possesses protein kinase C regulating activity.

As recommended by the PTO, applicant has modified the term “fragment” to specify that such fragment possesses protein kinase C regulatory activity. Given that the present application identifies two fragments from rat BVR and two fragments from human BVR that possess protein kinase C regulatory activity, consensus sequences of SEQ ID NO: 16 and 17, as well as how one of ordinary skill in the art can identify other fragments of mammalian BVR that possess such activity (see Example 3), applicant submits that one of ordinary skill in the art is fully able to identify and use such fragments in accordance with the presently claimed invention.

Therefore, the rejection of claims 68-70 and 74-76 for lack of enablement is improper and should be withdrawn.

The rejection of claims 1-8 and 69-75 under 35 U.S.C. § 112, first paragraph, lack of enablement is rendered moot with respect to claims 1-8 and is respectfully traversed

with respect to claims 69-75. (Applicant notes that the arguments asserted against claims 69-75 would appear also to apply to independent claim 68 and, therefore, applicant has treated this as a typographical error and has responded to the rejection accordingly.

. The PTO has asserted that the present application fails to provide sufficient enablement for in vivo use of BVR or fragments thereof active against protein kinase C. For substantially the same reasons set forth in applicant's prior response, applicant respectfully disagrees.

The present application identifies a number of techniques for introducing BVR into a patient, including (among others) liposome delivery, BVR-conjugates, and BVR chimera (see page 42, line 7 to page 44, line 4). These approaches can be utilized to deliver mammalian BVR (or a fragment thereof with protein kinase C regulatory activity or a polypeptide comprising the amino acid sequence of SEQ ID NO: 16 or 17) via various administration routes (see page 45, lines 24-32). By way of example, such mammalian BVR administration can be performed for purposes of regulating PKC activity in any one of a number of conditions in which PKC has a demonstrated role in disease pathology (see page 24, line 30 to page 25, line 2). Thus, the present application provides a description of in vivo uses for BVR (or a fragment thereof with protein kinase C regulatory activity or a polypeptide comprising the amino acid sequence of SEQ ID NO: 16 or 17).

As noted in applicant's prior response submitted on August 20, 2002, BVR is not the first compound ever disclosed to have a regulatory effect on PKC. In fact, much is known in the art about the cellular activities of PKC and its regulatory elements. For example, it is widely known that PKC plays an important role in cell-cell signaling, gene expression, the control of cell differentiation and growth, cancer development, and functioning of the central nervous system. Targeting the activity of PKC for regulatory effects is also widely known in the art. In particular, PKC inhibitors have been shown to prevent the damage seen in focal and central ischemic brain injury and brain edema (Hara et al., J. Cereb. Blood Flow Metab. 10:646-653 (1990) (copy attached as Exhibit A to August 20, 2002 response). It is also known that inhibitors of PKC are effective in preventing tumor growth in animals (Meyer et al., Int. J. Cancer 43:851-856 (1989) ("Meyer") (copy attached as Exhibit B to August 20, 2002 response).

Meyer, in particular, demonstrates the correlation between *in vitro* inhibition of protein kinase C activity with *in vivo* inhibition of protein kinase C activity using intraperitoneal administration of a protein kinase C inhibitor (designated CGP 41 251) to contact bladder carcinoma xenografts in athymic nude mice (see page 853). Given that

protein kinase C has previously been demonstrated to interact with compounds that regulate its activity both *in vitro* and *in vivo*, one of ordinary skill in the art would expect other *in vitro*-demonstrated regulators of protein kinase C activity to behave similarly. Example 3 of the present application demonstrates that protein kinase C activity can be regulated *in vitro* by BVR as well as fragments thereof possessing protein kinase C regulatory activity.


Given the results of Meyer and Example 3 of the present application, one of ordinary skill in the art would be fully able to prepare and administer a mammalian BVR (or a fragment thereof with protein kinase C regulatory activity or a polypeptide comprising the amino acid sequence of SEQ ID NO: 16 or 17) for purposes of regulating protein kinase C activity. For the reasons noted above, one of ordinary skill in the art would fully expect such *in vivo* administration to be successful in regulating protein kinase C activity. Therefore, the rejection of claims 68 and 69-75 for lack of enablement is improper and should be withdrawn.

The rejection of claims 7-9 and 74-76 under 37 C.F.R. § 1.75 for double patenting is respectfully traversed in view of the above amendments.

In view of all of the foregoing, applicant submits that this case is in condition for allowance and such allowance is earnestly solicited.



Respectfully submitted,

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☐ 1: NP_080954. biliverdin reduct...[gi:27764877]

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LOCUS Blvra 295 aa linear ROD 07-APR-2003
 DEFINITION biliverdin reductase A; biliverdin reductase [Mus musculus].
 ACCESSION NP_080954
 VERSION NP_080954.2 GI:27764877
 DBSOURCE REFSEQ: accession [NM_026678.2](#)
 KEYWORDS .
 SOURCE Mus musculus (house mouse)
 ORGANISM [Mus musculus](#)
 Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
 Mammalia; Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
 REFERENCE 1 (residues 1 to 295)
 AUTHORS Whitby, F.G., Phillips, J.D., Hill, C.P., McCoubrey, W. and Maines, M.D.
 TITLE Crystal structure of a biliverdin IXalpha reductase enzyme-cofactor complex
 JOURNAL J. Mol. Biol. 319 (5), 1199-1210 (2002)
 MEDLINE [22075337](#)
 PUBMED [12079357](#)
 REFERENCE 2
 AUTHORS The FANTOM Consortium and the RIKEN Genome Exploration Research Group Phase I & II Team.
 TITLE Analysis of the mouse transcriptome based on functional annotation of 60,770 full-length cDNAs
 JOURNAL Nature 420, 563-573 (2002)
 COMMENT PROVISIONAL REFSEQ: This record has not yet been subject to final NCBI review. The reference sequence was derived from [AK010847.1](#).
 On Jan 16, 2003 this sequence version replaced gi:[21311977](#).
 FEATURES
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ORIGIN

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//
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EXHIBIT B

Search Results of the Multiple Sequence Alignment Engine:

```
000001:          folded Alignments  (max extent = 295 columns)
000002: *****
000003: Mna EPeRKFGVVVGVRAGSVFmRDLrn Php Ss AFLNLIGfVSRRELGSi Dg Vq QISLEDALs SQEve VAYICs ESSSH
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000006:
000007:
000008: *****
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000013:
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